c) evaporating the volatile solvent from the homogeneous solution;

wherein the volatile solvent is present in the formulation in amounts between 40-80%

wherein said volatile solvent is selected from the group consisting of isopropyl alcohol and denatured ethyl alcohol.

9. A method for applying a topical anesthetic to an area of skin, the method comprises the steps of:

a) mixing from about 40-80% of alcohol with a mixture containing:
from about 3-40% of lidocaine;
from about 0.5 to about 2.0%, preferably about 1.5% thickener;
from about 0.5 to about 2.0%, preferably about 1.5% emulsiifer; and
the balance being a lipophilic base;

b) applying the homogeneous solution into the area of skin to be treated; and

c) evaporating the volatile solvent from the homogeneous solution;

wherein said topical anesthetic rapidly penetrates the skin surface at said skin

wherein said volatile solvent is selected from the group consisting of isopropyl alcohol and denatured ethyl alcohol.

13. A method of obtaining topical anesthesia in mammals by way of topical application, said method comprising administering a formulation comprising a mixture of lidocaine in a lipophilic base dissolved in 40-80% alcohol

wherein said alcohol is selected from the group consisting of isopropyl alcohol and denatured ethyl alcohol.

14. A method for applying a topical anesthetic to an area of skin, the method comprising the steps of:

a) incorporating an anesthetic in a lipophilic base into a volatile solvent to form a homogeneous solution;
b) applying the homogeneous solution into the area of skin to be treated; and
c) evaporating the volatile solvent from the homogeneous solution;

wherein the volatile solvent is present in the formulation in amounts between 40-80%

wherein said volatile solvent is selected from the group consisting of isopropyl alcohol and denatured ethyl alcohol

wherein the anesthetic is a eutetic mixture of lidocaine and prilocaine.

REMARKS

Review and reconsideration of the Office Action of June 5, 2002, is respectfully requested in view of the above amendment and the following remarks.

Claim 5 has been canceled. The subject matter of Claim 5 has been added to Claims 1, 9, and 13-14. No new matter has been introduced to the claims.

Applicant is submitting herewith a Declaration under 37 C.F.R. §1.132 to point out a further difference between the anesthetics of the present invention and the aesthetics of the cited prior art. Applicant respectfully requests that the Examiner consider the attached Declaration.

Applicant would like to point out to the Examiner that the claims are directed to method claims, thus all the steps of the Claims of the present invention must be taught in order to teach the present invention.

Applicant notes that the Sipos reference fails to teach: 1) incorporating an anesthetic in a lipophilic base into a volatile solvent, and 2) the step of evaporating the alcohol.

Nowhere in the reference is an indication that the local anesthetic is incorporated in **a lipophilic base (oil base)**. Furthermore, the reference does not provide any teaching regarding a **lipophilic** base. On the contrary, the Sipos reference teaches a formulation containing from **20% to 40% of water.** Thus the Sipos reference is teaching away from the present claims.

The selection of a lipid soluble base is not a mere choice. A base, which is lipid soluble, has a rapid onset of anesthesia since it enters the lipo-protein nerve membrane preventing the depolarization and ion exchange involved in stimulus conduction.

Applicant will also like to ask the Examiner how does a formulation containing 20 to 40% of water evaporate?

Applicant notes that the Castillo reference fails to teach the step of **evaporating the volatile solvent** from the homogeneous solution. The reference requires the use of a higher aliphatic alcohol (C8-18 or an ester). The present invention uses a volatile solvent such as isopropyl alcohol or denatured ethyl alcohol. **A C8-18 alcohol as a long chain alcohol cannot be considered as a low carbon alcohol.** See the Results of the evaporation test disclosed in the attached Declaration.

Furthermore, the reference does not teach or even suggest the use of a penetration enhancer.

Combining the references

Basically:

1) The Sipos reference requires **20% to 40% of water** in his formulation.

2) The Castillo reference requires a **lipophilic base**. According to the Webster Dictionary, "Lipophilic" is defined as having an affinity for, tending to combine with, or capable of, **dissolving in lipids** (oil, fat).

In Castillo, column 5, lines 52-55, is an indication that the lipophilic base must be **hydrophobic**. According to the Webster Dictionary, "hydrophobic" means having an aversion to water.

Any person skilled in the art would know that a water-based composition cannot be considered as capable of dissolving in oil. (Knowledge of Basic Chemistry).

Thus, incorporating the lipophilic base of the Castillo reference into the water-based composition of Sipos **is not possible. Thus, the Castillo and Sipos references are teaching away from each other.**

How can two references that are teaching away from each other be combined?

Present Invention

First, Applicant discusses the basis for, and the distinguishing features of the present invention.

The use of topical anesthetics has been found useful for superficial skin procedures. Topical anesthetics act via a loss of sensation in the localized area of administration in the body. The mechanism by which topical anesthetics induce their effect,

while not having been determined definitively, is generally thought to be based upon the ability to topically interfere with the initiation and transmission of a nerve impulse, e.g., interfering with the initiation and/or propagation of a depolarization wave in a localized area of nerve tissue. But unfortunately, the use of local anesthesia of intact skin for minor procedures is not achieved until at least 60 minutes following application. For more invasive procedures, such as split skin graft harvesting, at least two hours may be required. This delay in onset is a significant disadvantage, as it is a great inconvenience for both patients and medical staff. Such delay is particularly a problem in the area of pediatrics, where any additional time spent awaiting treatment only contributes to the anxiety of the patient.

Another disadvantage of the prior art is that, for deep penetrative effect, it is necessary that the cream be applied under an occlusive dressing. Specifically, a bilayer of laminate and absorbent cellulose is taped to the area of the skin to be anesthetized. Such a dressing is inconvenient and messy.

Skin is a structurally complex, relatively thick membrane. Molecules moving from the environment into and through intact skin must first penetrate the stratum corneum and any material on its surface. They must then penetrate the viable epidermis, the papillary dermis, and the capillary walls into the blood stream or lymph channels to be so absorbed; molecules must overcome a different resistance to penetration in each type of tissue. Transport across the skin membrane is thus a complex phenomenon. However, it is the cells of the stratum corneum, which present the primary barrier to absorption of topical compositions or transdermally administered drugs.

It has now been surprisingly discovered that the above problems can be overcome, and that a topical, transdermal anesthetic comprising lidocaine can be surprisingly enhanced, by the addition of a high proportion of a volatile carrier/penetration enhancer, preferably a low carbon alcohol, to the anesthetic formulation.

The present invention concerns a method for applying a topical anesthetic to an area of skin, the method comprising the steps of:

a) incorporating an anesthetic in **a lipophilic base** into a volatile solvent to form a homogeneous solution;

b) applying the homogeneous solution into the area of skin to be treated; and

c) **evaporating** the volatile solvent from the homogeneous solution;

wherein the volatile solvent is present in the formulation in amounts between 40-80%

wherein said volatile solvent is selected from the group consisting of isopropyl alcohol and denatured ethyl alcohol.

Upon application to the skin of a patient, and prior to evaporating, the alcohol acts as a penetration enhancer that increases the permeability of the skin, preparing the skin so that the rate at which the anesthetic drug diffuses through the skin and enters the tissues and bloodstream will be increased. The alcohol alters the physiochemical nature of the stratum corneum to reduce its diffusional resistance.

Then, after the skin resistance has been altered, after the skin is initially rendered cool and somewhat anesthetized, and after much of the alcohol has evaporated, the kinetics of the formulation change so that, as the proportion of remaining alcohol is reduced, **a more concentrated anesthetic formulation**

remains present on the skin, which brings about a more advanced level of anesthetization.

Thus, by using the formulation of the present invention, the delivery rate of the anesthetic is markedly enhanced, the method of administration remains simple, the incidence of side effects associated with many penetration enhancers is reduced or eliminated, topical irritation is avoided, and the comfort level of the patient is increased as the patient has the perception that the formulation is taking effect.

Office Action

Turning now to the Office Action in greater detail, the paragraphing of the Examiner is adopted.

Paragraphs 1 and 2 (Obviousness)

The Examiner rejects Claims 1-14 under 35 U.S.C. 103(a) as being obvious over Sipos (US 5,993,836) in view of Castillo (US 5,993,836).

The Examiner indicates that the claims read on a method of applying local anesthetics in lipophilic base in lower alcohols to provide local anesthesia.

The position of the Examiner regarding the Sipos and Castillo references can be found on pages 2-5 of the Office Action.

Applicant respectfully traverses.

Regarding the Sipos reference

Applicant would like to point out to the Examiner that the present claims are **method claims**, thus in order for a reference to teach the present invention, it must disclose **all the steps** required by the method.

Compared with present Claim 1, the Sipos reference fails to teach the steps of:

1) **evaporating the volatile solvent** from the homogeneous solution; and
2) incorporating an anesthetic in a **lipophilic base** into a volatile solvent to form a homogeneous solution.

Regarding point 1

Applicant notes that in Column 9, lines 10-14, and lines 30-33, the reference teaches that the formulation contains from about 10 to 50% of water, preferably from about 20% to 40% of water. See examples 2-11.

How does a formulation containing that amount of water evaporate?

Applicant also notes that the reference uses alcohol as a vehicle and not as a penetration enhancer. Furthermore, the reference suggested even the possibility of using water as a vehicle.

The Sipos reference uses as penetration enhancer a primary, secondary, and tertiary aliphatic alcohols having 5 to 10 carbons; or a cyclohexyl substituted alkanol; or a phenyl alkanol.

As indicated on page 4 of the specification of the present invention, the use of penetration enhancers has been known by the prior art. Unfortunately, the uses of the known penetration enhancers are associated with disadvantages.

The Sipos reference does not overcome the disadvantages of penetrating enhancer known by the prior art. For one, the

penetration enhancer is co-administered with the anesthetic **(in our invention the penetration enhancer quickly evaporates)**, thus the penetration enhancer passes through the patient's skin at the same time the drug does. This can lead to side effects related directly to the penetration enhancers.

Another disadvantage is that the addition of penetration enhancers changes the concentration of the drug, thus the acceptable delivery rate of the medicament that needs to be delivered through the skin is lowered, and the anesthetic will take longer time to act.

Also, the use of cyclohexyl substituted alkanol or a phenyl alkanol (organic solvents) as penetration enhancers may produce an alteration on the character of the anesthetic. In addition, it is possible that the enhancers can interact with the patient's skin and cause irritation. As can be seen, the Sipos reference does not overcome the problem of the prior art.

The present invention overcomes the problems presented by the prior art by using **a high concentration of a volatile penetration enhancer, a low carbon alcohol, to the anesthetic formulation.**

Upon application to the skin of a patient, and prior to evaporating, the alcohol acts as a penetration enhancer that increases the permeability of the skin, preparing the skin so that the rate at which the anesthetic drug diffuses through the skin and enters the tissues and bloodstream will be increased. The alcohol alters the physiochemical nature of the stratum corneum to reduce its diffusional resistance.

Then, after the skin resistance has been altered, after the skin is initially rendered cool and anesthetized, and after much of the alcohol has evaporated, the kinetics of the formulation

change so that, as the proportion of remaining alcohol is reduced, a more concentrated anesthetic formulation remains present on the skin, which brings about a more advanced level of anesthetization.

The present invention requires the use of a low carbon alcohol because low carbon alcohols have a relatively low value of heat of vaporization, which makes them able to evaporate QUICKLY at room temperature, avoiding the penetration of high concentration of the alcohol onto the skin.

Regarding point 2

The step of incorporating the anesthetic to a lipophilic base is very important. It is believed that **the base, which is lipid soluble,** has a rapid onset of anesthesia since it enters the lipo-protein nerve membrane preventing the depolarization and ion exchange involved in stimulus conduction. Thus, adding water (Sipos) to the formulation will teach away from the present invention.

Nowhere in the reference is an indication that the local anesthetic is incorporated in a lipophilic base as claimed in Claim 1. Furthermore, the reference does not provide any teaching regarding a lipophilic base.

As indicated in the specification of the present patent application, the lipophilic based formulation of the present invention is one which **contains no, or substantially no, aqueous component or aqueous functional-equivalent.** As lipophilic materials, an oleaginous material such as petrolatum, mineral oil thickened or gelled with polyethylene, high molecular weight

paraffin waxes, mono and diglycerides of fatty acids gelled with high molecular weight fatty acids or polyamide complex of hydroxystearate, propylene glycol isostearate or isostearyl alcohol gelled with high molecular weight fatty acids and mixtures thereof may be used.

Claim 9 and 13 are novel for the same reasons set forth for Claim 1.

Applicant notes that the Sipos reference does not mention the possibility of having an anesthetic comprising an **eutetic mixture** of lidocaine and prilocaine as required by Claim 14. Furthermore, the reference does not teach or suggest the use of a mixture of lidocaine and prilocaine as anesthetic.

Regarding the Castillo Reference

Applicant notes that the reference is silent regarding the use of a penetration enhancer to provide a rapid penetration of the anesthetic.

Applicant notes that compared with Claim 1, the reference fails to teach the step of **evaporating the volatile solvent** from the homogeneous solution. The reference does not use a penetration enhancer. Furthermore, the reference requires the use of a higher aliphatic alcohol (C8-18 or an ester). The present invention uses a volatile solvent such as a low carbon alcohol. **A C8-18 alcohol cannot be considered as a low carbon alcohol.**

Applicant would like to direct the Examiner attention to the results of the evaporation test disclosed in the attached Declaration.

Applicant also notes that the reference indicates (prior to Example 1) that:

"the formulation of the present invention **may be applied to a carrier of paper, patches, or pads,** as disclosed in U.S. Pat. Nos. 4,529,601 (Broberg, et al.) and 4,562,060 (Broberg, et al.), so that the cellulose fibers of the pre-formed carrier is soaked with the formulation. Also, the present formulation may be prepared as a stick formulation suitable for delivery of pharmacologically-active compounds, as disclosed in U.S. Pat. No. 5,622,993 (McGinity, et al.)."

Thus, the reference does not recognize the importance of the step of evaporating the volatile solvent.

Combining the references

Basically:

1) The Sipos reference requires 20% to 40% of water in his formulation.
2) The Castillo reference requires a lipophilic base. According to the Webster Dictionary, "Lipophilic" is defined as having an affinity for, tending to combine with, or capable of dissolving in lipids (oil, fat).

Also in Castillo column 5, lines 52-55, is an indication that the lipophilic base must be hydrophobic. According to the Webster Dictionary, "hydrophobic" means having an aversion to water.

Any person skilled in the art would know that a water-based composition cannot be considered s capable of dissolving in oil. (Knowledge of Basic Chemistry).

Thus, incorporating the lipophilic base of the Castillo reference into the water-based composition of Sipos, **it is not possibl . Thus, the Castillo refer nce is teaching away from the** Sipos reference.

References Are Not Properly Combinable or Modifiable if Their Intended Function is Destroyed

A §103 rejection based upon a modification of a reference that destroys the intent, purpose, or function of the invention disclosed in the reference, is not proper. In short, there would be no technological motivation for engaging in the modification or change. To the contrary, there would be a disincentive. In re Gordon 221 USPQ 1125 (Fed. Cir 1984).

The Examiner must be able to point to something in the prior art that suggests in some way a modification of a particular reference or a combination with another reference in order to arrive at the claimed invention. Absent such a showing in the prior art, the Examiner has impermissibly used the Applicant's teaching to hunt through the prior art for the claimed elements and combine them as claimed. In re Laskowski 10 USPQ 2d 1397, 1398 (Fed. Cir. 1989).

Accordingly, withdrawal of the rejections is respectfully requested.

Favorable consideration and early issuance of the Notice of Allowance are respectfully requested. Should further issues remain prior to allowance, the Examiner is respectfully requested to contact the undersigned at the indicated telephone number.

Respectfully submitted,

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